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On the Inappropriateness of Noninvasive Multidetector Computed Tomography Coronary Angiography to Trigger Coronary Revascularization

A Comparison With Invasive Angiography

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Objectives Our purpose was to evaluate the appropriateness of multidetector computed tomography angiography (MDCTA) as an anatomical standard for decision making in patients with known or suspected coronary artery disease.

Background Although correlative studies between MDCTA and coronary angiography (CA) show good agreement, MDCTA visualizes plaque burden and calcifications well before luminal dimensions are encroached.

Methods Pressure-derived fractional flow reserve (FFR) was obtained in 81 patients (116 vessels) who underwent both CA and MDCTA. Segments were visually graded for stenosis severity as: G0 = normal, G1 = nonobstructive (<50% diameter reduction), and G2 = obstructive (≥50% diameter reduction).

Results Concordance between segmental severity scores by MDCTA and CA was good (k = 0.74; 95% confidence interval: 0.56 to 0.92). Diagnostic performance of MDCTA for detection of functionally significant stenosis based on FFR was low (sensitivity 79%; specificity 64%; positive likelihood ratio 2.2; negative likelihood ratio 0.3). Revascularization was considered appropriate in the presence of reduced FFR (≤0.75). Decision making based on MDCTA guidance would result in revascularization in the absence of ischemia in 22% of patients (18 of 81) and inappropriate deferral in 7% (6 of 81), while revascularization in the absence of ischemia would be 16% (13 of 81) and inappropriate deferral 12% (10 of 81) with decisions guided by CA. Combined evaluation of stenosis severity using both anatomy (with either CA or MDCTA) and function (with FFR) yields the highest proportion of appropriate decisions: 90% and 91%, respectively (p = 0.0001 vs. CA only, p = 0.0001 vs. MDCTA only).

Conclusions Similar to CA, anatomical assessment of coronary stenosis severity by MDCTA does not reliably predict its functional significance. (J Am Coll Cardiol Intv 2009;2:550–7) © 2009 by the American College of Cardiology Foundation

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Visual estimation of coronary stenosis severity during invasive coronary angiography (CA) does not predict its hemodynamic significance, even when performed and analyzed by experienced cardiologists (1,2). Yet coronary revascularization using stented angioplasty is triggered off increasingly often by anatomical imaging (3,4). This trend is likely to increase with the availability of noninvasive multidetector computed tomography coronary angiography (MDCTA). Although correlative studies between MDCTA and CA show good agreement (5,6), MDCTA visualizes plaque burden and calcifications well before luminal dimensions are encroached (7–9). As a result, the information content of MDCTA is broader than that provided by CA, which may improve the decision whether or not to proceed with revascularization.

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The purpose of this prospective study was: 1) to compare the assessment of coronary stenosis severity by MDCTA versus invasive angiography in patients with known or suspected coronary artery disease (CAD); and 2) to evaluate the appropriateness of using MDCTA as the anatomical substrate for clinical decision making with respect to revascularization. Appropriateness of revascularization was assessed by pressure-derived fractional flow reserve (FFR), a reliable invasive index of stenosis hemodynamic significance. FFR expresses the maximum achievable blood flow to the myocardium supplied by a stenotic artery as a fraction of normal maximum flow (10,11). An abnormal value ≤0.75 identifies stenosis that is associated with inducible ischemia (12,13) that can be relieved by stented angioplasty or bypass grafting. Operators were encouraged to base the treatment strategy on FFR results, but final individual decisions were taken on the basis of all available data, at their discretion.

Methods

Patient selection. The study population consisted of 88 patients in whom MDCTA was implemented in the diagnostic workup of chest pain, of which 7 patients were excluded because of uninterpretable or technically poor MDCTA studies. From the remaining 81 patients, 39 had stable angina (48%) and 42 (52%) had atypical chest pain. Selected patients were identified prospectively at the time of their first visit at the outpatient clinic. Exclusion criteria were as follows: atrial fibrillation, creatinine clearance below 30 ml/min, and allergy to iodinated contrast agents. Only 15 patients (19%) were known to have CAD from prior history. In the 61 (81%) patients with suspected CAD, the pre-test probability for obstructive CAD was calculated using the Duke clinical risk score, which includes type of chest pain, age, sex, and traditional risk factors (14,15). Subjects are classified as low, intermediate, or high risk. Conventional CA was performed according to local practice 26 ± 11 days after the MDCTA. Follow-up was performed to evaluate the clinical event rates: new revascularization after the index procedure, new angina onset, myocardial infarction, and cardiac death. The study protocol was approved by the institutional ethics committee and patients gave informed consent for participation and data collection.

CA and FFR assessment. Distal coronary pressure measurement was performed with a 0.014-inch pressure guidewire (Radi Medical Systems, Uppsala, Sweden). The wire was introduced through a 6-F guiding catheter, calibrated, advanced into the coronary artery, and positioned in the distal vessel beyond the stenosis as previously described (11). Adenosine was administered to induce maximum hyperemia, either intravenously (140 μg/kg/min) or intracoronary (at least 15 μg in the right or 20 μg in the left coronary artery) (11,16,17). FFR was calculated as the ratio of mean hyperemic distal coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter. The measurement was performed twice, and FFR was taken as the average of both measurements. Interrogated coronary vessels (n = 116) were segmented according to the American Heart Association classification (18). Stenosis severity was graded by independent experienced observers unaware of FFR results according to the following scoring system:

- Grade 0: entirely normal vessel segment, no plaque and no wall irregularities
- Grade 1: CAD present, nonobstructive plaque, <50% diameter reduction
- Grade 2: obstructive stenosis, ≥50% diameter reduction

Abbreviations and Acronyms

CA = coronary angiography

CAD = coronary artery disease

FFR = fractional flow reserve

LAD = left anterior descending coronary artery

MDCTA = multidetector computed tomography angiography

PCI = percutaneous coronary intervention

MDCTA protocol. After determination of the coronary artery calcium score (24 × 1.2 collimation, 330-ms gantry rotation time, 0.2 pitch, 3-mm slice thickness, 120-kV tube voltage, 145-mAs tube current), MDCTA was performed using a Sensation 64 scanner (Siemens Medical Solutions, Forchheim, Germany). Scanning parameters were 64 × 0.6-mm collimation, 330-ms rotation time, 3.8-mm/rotation table feed, 120-kV tube voltage, and 850-mAs tube current. Axial images were reconstructed with a slice thickness of 0.75 mm and a reconstruction increment of 0.4 mm, using a medium sharp convolution kernel at 5% intervals over the entire R-R cycle using a single segment reconstruction algorithm. Before the scan, sublingual nitroglycerine was administered, and patients with a baseline heart rate >65 beats/min were given beta-blockers (metoprolol 25 to 100 mg orally before examination, supplemented by intravenous administration as required). A

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Table 1. Patient Demographics

	Total (n = 81)	Suspected CAD: Low Risk (n = 14)	Suspected CAD: Intermediate Risk (n = 23)	Suspected CAD: High Risk (n = 24)	Known CAD (n = 20)	p Value
Men	60 (74)	9 (64)	16 (70)	21 (88)	14 (70)	NS
Age (yrs)	62 ± 11	52 ± 13*	61 ± 9	65 ± 9	67 ± 9	<0.001
BMI (kg/m^2)	28 ± 5	30 ± 7	28 ± 4	28 ± 4	26 ± 3	NS
HR (beats/min)	71 ± 11	77 ± 18	66 ± 8	71 ± 10	74 ± 12	NS
Risk factors						
Smoker	32 (40)	0	10 (43)	10 (41)	11 (55)	NS
Diabetes mellitus	14 (17)	3 (21)	2 (8)	4 (17)	4 (20)	NS
Hypertension	39 (48)	9 (64)	9 (39)	11 (46)	11 (40)	NS
Hyperlipidemia	41 (51)	5 (36)	16 (70)	9 (38)	10 (50)	NS
Family history of CAD	40 (49)	8 (57)	10 (43)	12 (50)	11 (55)	NS
Calcium score (Agatston)	518 ± 578	138 ± 189*	577 ± 546	643 ± 749	521 ± 396	0.02
Clinical presentation						
Stable angina	39 (48)	1 (7)*	7 (30)	20 (83)	10 (50)	<0.0001
Atypical chest pain	42 (52)	13 (93)*	16 (70)	4 (17)†	10 (50)	<0.0001
Duke score (%)		15 ± 6*	49 ± 14‡	89 ± 7	—	<0.0001
Medical history						
Previous PCI	7 (9)	0	0	0	7 (35)	<0.0001
Previous AMI	6 (7)	0	0	0	6 (30)	<0.0001
MVD by CA	28 (35)	1 (7)*	7 (30)†	8 (29)	13 (65)	<0.01

Values are n (%) or mean ± SD. *p < 0.01 versus intermediate-risk, high-risk, and known coronary artery disease (CAD) groups; †p < 0.05 versus known CAD group; ‡p < 0.01 versus high-risk group.
AMI = acute myocardial infarction; BMI = body mass index; CA = coronary angiography; HR = heart rate; MVD = multivessel disease; PCI = percutaneous coronary intervention.

bolus (on average 90 ml at 5 ml/s) of contrast material (iomeprol, 816.5 mg/ml [Iomeron 400, Bracco Altana Pharma, Konztanz, Germany]) was injected intravenously followed by a 50-ml saline flush. After a scan delay, the scan started automatically when the density in the aortic root reached a density value of 100 HU. All the datasets were evaluated offline on an image analysis workstation (TeraRecon Inc., San Mateo, California). MDCTA data were evaluated on axial plane source images, on curved multiplanar reconstruction, and on different maximal intensity projections.

Coronary vessel segmentation was matched with CA, and stenosis severity was graded as described in the preceding text by independent experienced observers unaware of grading results on CA.

Statistical analysis. The diagnostic performance of MDCTA and CA for the detection of functionally significant CAD as defined by FFR ≤0.75 is presented as sensitivity, specificity, positive and negative predictive values with the corresponding confidence intervals, and positive and negative likelihood ratios. Comparisons between MDCTA and FFR or CA and FFR were performed for each interrogated vessel. Continuous variables are expressed as means and standard deviation. Differences in means among groups were analyzed by a 2-sided *t* test or by 1-way analysis of variance using a Tukey-Kramer test to compare all pairs. Categorical variables are expressed as absolute numbers and percentages. Interobserver and intraobserver variability of the score grading by MDCTA and CA and agreement between techniques were tested by kappa statistics. False negatives were defined as vessels with abnormal FFR but nonobstructive stenosis (grade 0 to 1). False positives were defined as vessels with normal FFR but obstructive stenosis (grade 2).

The proportion of patients with consistent or inconsistent treatment decisions that are in accordance with test results is shown as absolute number and percentage for each technique. Unpaired and paired comparison between proportions uses the chi-square and McNemar tests, respectively. Appropriateness by FFR refers to revascularization of hemodynamically significant stenoses and deferral of nonsignificant stenoses, meaning that appropriateness is based on treatment decisions that are in accordance with functional test results. Any other decision will be called inappropriate. Operators were encouraged to base the treatment strategy on FFR results, but final individual decisions were taken on the basis of all available data, at their discretion. Kaplan-Meier curves are comparing major adverse cardiac event rates between inappropriate/appropriate treatment guided by MDTCA and FFR, respectively. Comparison between the curves uses the Gehan-Breslow-Wilcoxon test.

Results

Patient demographics are shown in Table 1. Obstructive CAD (grade 2) was diagnosed in 37 (44%) patients by CA

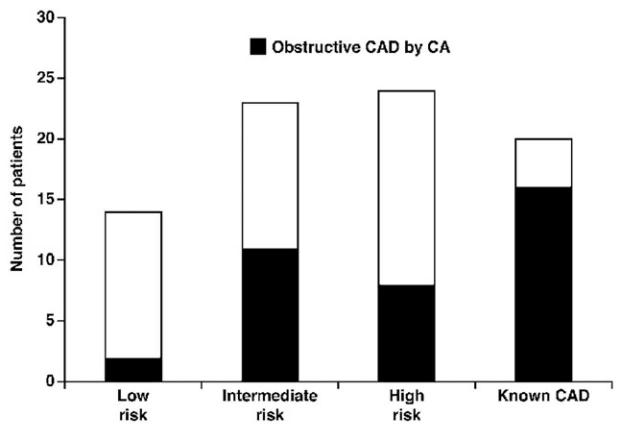

Figure 1. Obstructive CAD by Angiography per Category of Duke Risk Score

Distribution of study population according to the Duke risk score before multidetector computed tomography angiography and invasive evaluation. **Solid portion of bars** represent the proportion of patients shown to have obstructive coronary artery disease (CAD) by invasive coronary angiography (CA).

and in 43 (55%) patients by MDCTA, with a concordance rate of 97% per vessel and 92% per patient. The distribution of study population according to the Duke risk score and presence of obstructive CAD by CA is shown in Figure 1. The vessel of interest (n = 116) was the left anterior descending in 82 (71%), the left circumflex or marginal branch in 19 (15%), and the right coronary artery in 17 (14%). The number of coronary segments assessed by visual scoring of disease severity was 334. The concordance between segmental severity scores by MDCTA and CA was good (k = 0.74; 95% confidence interval: 0.56 to 0.92).

Appropriateness of therapeutic decisions is shown in Figure 2. There were 51 patients with appropriate treatment guided by MDCTA, of whom there were 30 patients with obstructive stenoses treated by percutaneous coronary intervention (PCI) and 21 patients with nonobstructive stenoses treated by conservative medical therapy. There were 29 patients with inappropriate treatment guided by MDCTA, of whom there were 12 patients with obstructive stenoses treated by conservative medical therapy and 17 patients with nonobstructive stenoses treated by PCI. There were 65 patients with appropriate treatment guided by FFR, of whom 28 patients with FFR ≤0.75 were treated by PCI and 37 patients with FFR >0.75 were treated by conservative treatment. There were 16 patients with inappropriate treatment by FFR, of whom 6 patients with FFR ≤0.75 were treated by conservative medical therapy and 10 patients with FFR >0.75 were treated by PCI.

Combining anatomical evaluation (with either CA or MDCTA) with functional evaluation of stenosis severity (using FFR) yields the highest proportion of appropriate decisions: 90% and 91%, respectively (p = 0.0001 vs. CA alone, p = 0.0001 vs. MDCTA alone).

Comparison between MDCTA and FFR. The diagnostic performance of MDCTA for the detection of functionally significant stenoses (FFR ≤0.75) was poor, yielding nondiagnostic positive likelihood ratios (Table 2, Fig. 3). Mean FFR was significantly (p < 0.01) lower between normal (grade 0) and diseased segments. However, individual datapoints show a wide overlap between intermediate (grade 1) and obstructive stenoses (grade 2) with a wide range of FFR values in grade 2 stenoses. The false negative rate was 6% (7 of 116), mostly located in the mid-distal segments of the left anterior descending coronary artery (LAD) (6 of 7, 86%). The false positive rate was 26% (30 of 116), with segments located predominantly in the LAD (19 of 30, 63%) or left circumflex coronary artery (6 of 30, 20%). Agatston coronary artery calcium score (excluding 1 outlier with a score above 10.000) was not different between true positive and false negative cases but significantly higher (p = 0.04) in false positive (723 [451 to 994]) than in true negative cases (357 [230 to 484]).

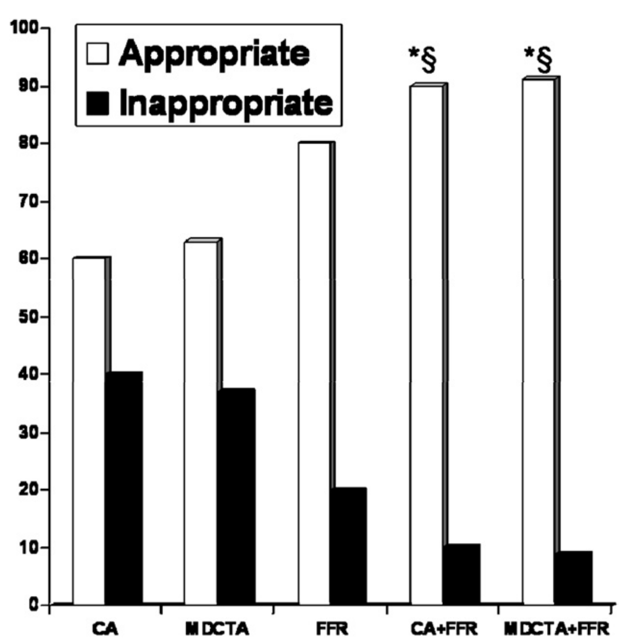

Figure 2. (In)Appropriateness of Treatment Decisions Guided by Anatomy, Function, or Both

Percentage of appropriate and inappropriate treatment decisions based on the result of individual or combined techniques: coronary angiography (CA), multidetector computed tomography angiography (MDCTA), fractional flow reserve (FFR), CA + FFR, MDCTA + FFR. Appropriateness by FFR is not 100% because individual decisions were taken on the basis of all available data, at the operator's discretion. Combined approaches are significantly different from both CA and MDCTA. *p < 0.001 versus CA; §p < 0.001 versus MDCTA.

Table 2. **Diagnostic Performance of MDCTA and CA for the Detection of Functionally Significant Stenosis Based on Pressure-Derived FFR Measurements**

	TP, n	TN, n	FP, n	FN, n	Sensitivity*, %	95% CI	Specificity*, %	95% CI	LR+*	LR−*
MDCTA										
All vessels	26	53	30	7	79	61–91	64	52–74	2.2	0.3
Per patient	24	33	18	6	80	61–92	65	51–78	2.3	0.3
CA										
All vessels	22	59	24	11	67	48–82	71	60–81	2.3	0.4
Per patient	20	38	13	10	67	47–83	75	60–86	2.6	0.4

*Multidetector computed tomography angiography (MDCTA) versus coronary angiography (CA), p value = NS.
CI = confidence interval; FFR = fractional flow reserve; FN = false negative; FP = false positive; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; TN = true negative; TP = true positive.

Comparison between CA and FFR. The diagnostic performance of CA for the detection of functionally significant stenosis (FFR $\leq$0.75) was poor, yielding nondiagnostic positive likelihood ratios (Table 2, Fig. 4). There was a significant difference in FFR values between intermediate (grade 1) and obstructive (grade 2) stenoses, with a marked overlap of the individual datapoints and a wide range of FFR values in grade 2 stenoses. The false negative rate was 10% (11 of 116), mostly located in the mid-distal segments of the LAD (9 of 11, 82%). The false positive rate was 21% (24 of 116), with segments located predominantly in the LAD (12, 50%) or left circumflex coronary artery (5 of 24, 21%).

Clinical outcome. During the mean follow-up time of 1.8 $\pm$ 0.3 years, 12 patients had new events: 7 presenting new angina requiring hospitalization and 5 requiring revascularization. New events occurred primarily in patients with inappropriate treatment by FFR: 1 with abnormal FFR that was not revascularized, and 4 patients with nonsignificant FFR that were revascularized. The event-free survival curves for patients with appropriate versus inappropriate treatment by MDCTA and by FFR, respectively, are shown in Figure 5. The event-free survival rate was significantly worse in the inappropriate versus the appropriate treatment group, as defined by FFR: 68 % versus 89%, respectively ($p = 0.02$).

Implications for selection of lesions for revascularization. Given the weak correlation between FFR and both MDCTA and CA, indications for revascularization purely based on anatomy will be inappropriate by FFR guidance in nearly 30% of patients (Figs. 3 and 4). Decision making based on MDCTA would result in revascularization in the absence of ischemia in 22% (18 of 81) and inappropriate deferral in 7% of cases (6 of 81). Decision making based on CA would result in revascularization in the absence of ischemia in 16% (13 of 81) and inappropriate deferral in 12% of cases (10 of 81). Decision making based on MDCTA will not result in significantly less revascularization in the absence of ischemia or inappropriate deferral than with CA. In patients inappropriately deferred by the operator despite abnormal

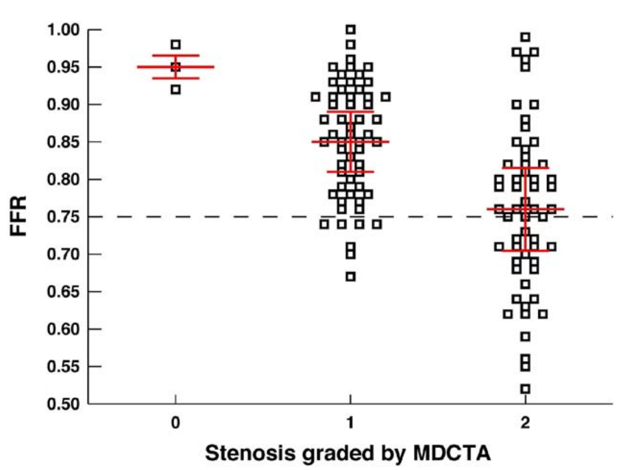

Figure 3. **Invasive Flow Reserve Versus Stenosis Severity by Noninvasive MDCTA**

Scatter plot showing a significant difference in FFR values for grade 0 ($p < 0.01$) stenoses by MDCTA compared with grade 1 and grade 2 stenoses. A wide range of FFR values is observed for grade 2 stenosis. Abbreviations as in Figure 2.

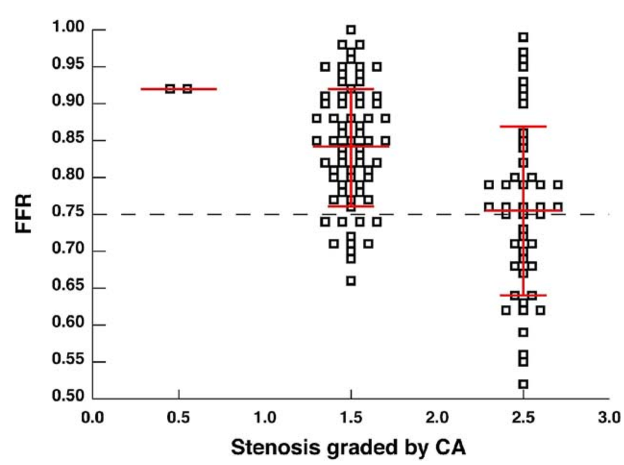

Figure 4. **Invasive Flow Reserve Versus Stenosis Severity by Invasive CA**

Scatter plot showing a significant difference in FFR values between grade 1 and grade 2 stenoses by CA ($p < 0.01$) with a wide range of FFR values for grade 2 stenosis. Abbreviations as in Figure 2.

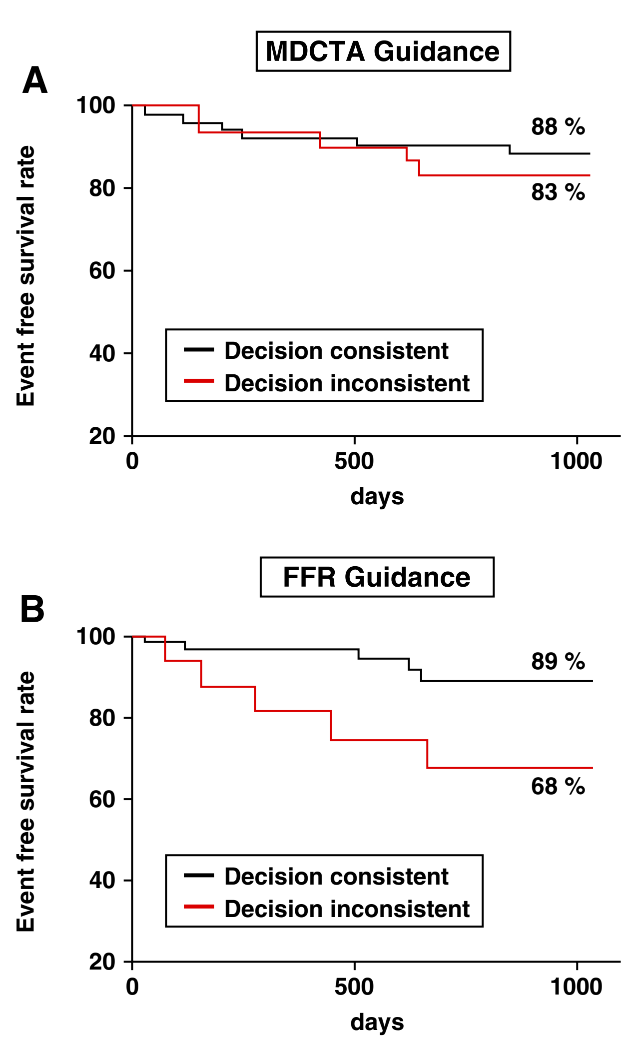

Figure 5. Impact of Consistency of Decision Making on Outcome

Event-free Kaplan-Meier curves between consistent and inconsistent treatment decisions based on MDCTA **(A)** or FFR **(B)** results. Consistent decisions are revascularization with abnormal or no revascularization with normal test results **(black lines)**. Inconsistent decisions are revascularization with normal or no revascularization with abnormal test results **(red lines)**. A significant difference ($p < 0.02$) in outcome is observed between inappropriate and appropriate revascularization using FFR guidance **(B)**. Abbreviations as in Figure 2.

FFR, reduced flow reserve was due to diffuse disease in nearly 40% of the cases, while focal stenosis eventually amenable to stented angioplasty was present in the remainder (Fig. 6).

Discussion

In patients with stable CAD, outcome-based trials (19) and guidelines (20) recommend revascularization in the presence of disabling symptoms or extensive stress-inducible ischemia. Although large cohort studies (21) have shown statistically significant correlations between stenosis severity assessed by quantitative CA and noninvasive or invasive functional testing, variability is such that one cannot rely on the coronary angiogram for clinical decision making in the individual patient. There are many reasons why the evaluation of stenosis severity may differ whether analyzed by CA or physiology. Selective CA does not account for the extent of downstream collateral supply or the size of the myocardial segment subtended by a given coronary artery. Diffuse luminal narrowing is common and precludes the selection of a “normal” reference segment (22).

Given the performance characteristics of the current 64-slice MDCTA, we hypothesized that this new coronary imaging modality would be more accurate than CA in identifying hemodynamically significant stenoses. Indeed, MDCTA is superior to CA by providing direct visualization of plaque load (23). Opacification of the coronary lumen by intravenous contrast delivery accounts for all sources of blood supply. Tomographic imaging allows multiplanar reconstructions that render the tridimensional structure of the coronary arteries and provides a more accurate description of eccentric stenoses.

Yet the present study shows an equally poor diagnostic performance of both imaging techniques, MDCTA and CA, for the detection of functionally significant CAD. The 26% false positive rate with MDCTA was associated with increased calcium scores. Arterial wall calcifications can be present from the early stages of atherosclerosis (24). The presence of calcifications causes blooming artifacts that increase plaque volume. With MDCTA, high coronary calcium load leads to stenosis overestimation and false positive results (25).

Clinical implications. Irrespective of mechanisms, this study demonstrates that indications for revascularization based solely on anatomy will be inappropriate in 21% (24 of 116) to 26% (30 of 116) of cases. As a matter of fact, the worst clinical outcome was seen in patients with inappropriate treatment according to FFR as a standard of reference. Because acute myocardial infarction and sudden death can proceed from plaque events at mildly obstructed sites, some physicians and patients fear to defer “treatment” of nonobstructive plaque, and preventive mechanical “plaque sealing” has been advocated. However, this hypothesis has not been properly investigated thus far (26,27). Instead, stented angioplasty of nonhemodynamically significant stenoses with an FFR >0.75 was shown not to improve the patient’s prognosis or symptoms, while consuming resources unnecessarily (12,13). These results of the DEFER (Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis) study (13) were confirmed by the larger FAME (Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Interventions) trial (28) showing improved outcome with reduced costs in patients with multivessel disease randomized to FFR-guided stented an-

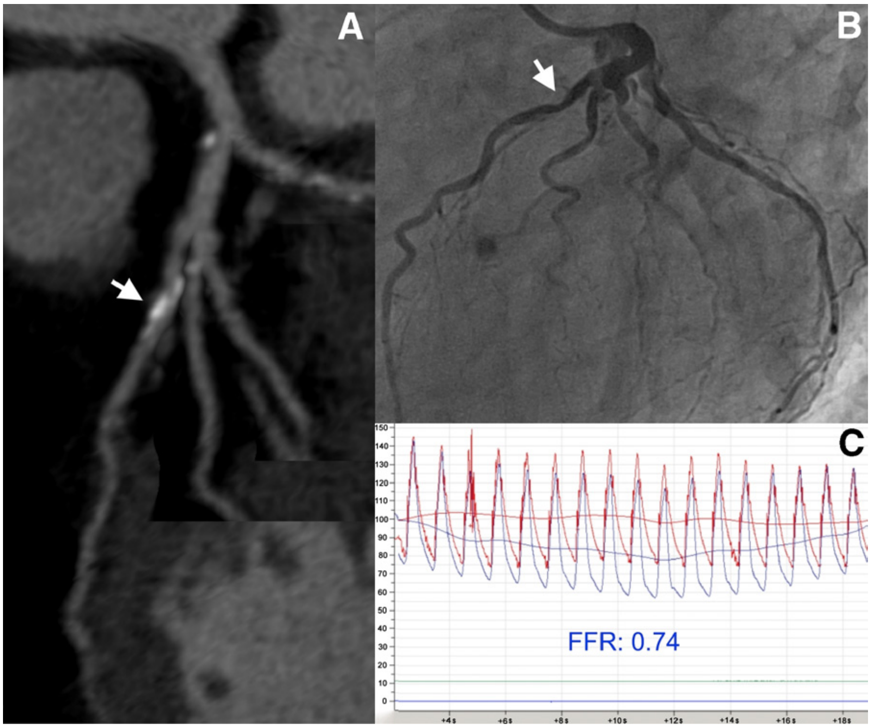

Figure 6. Inappropriate Deferral With Decision Making Based on Anatomy

Example of a false-negative stenosis, graded as nonobstructive (grade 1) both by multidetector computed tomography angiography **(A)** and coronary angiography **(B)** while fractional flow reserve (FFR) was significantly reduced **(C)**. Decision making driven by anatomy will result in inappropriate deferral of revascularization.

gioplasty, as opposed to intervention guided by anatomy only. These data are consistent with the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (19) of which a recently published substudy (29) indicates that revascularization improves outcome only when substantial ischemia is present before—and reduced by—revascularization. In the present clinically oriented study, revascularization decisions were left to the operator's discretion, which was in agreement with the results of anatomo-functional evaluation in 80% of cases (much higher than the 50% reported by Meijboom et al. [30]). Noninvasive coronary imaging by MDCTA has been recommended as a screening tool for identification of patients to be referred for revascularization (31). In accordance with recently issued guidelines (32), the present study invalidates any diagnostic strategy that would not incorporate functional testing for the presence of inducible ischemia, be it performed noninvasively before catheterization or during the invasive procedure using pressure-derived FFR (33).

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